

Commentary

Immunological Reflections on Asbestos

by Robert Burrell*

As a pulmonary immunologist interest in all forms of immune injury to the lung, I have had some experience with related minerals, such as silica and coal mine dust.

When compared to the immunologic aspects of silicosis or coal workers' pneumonitis (CWP), the bulk of the immunologic evidence concerning asbestosis is scanty and unimpressive. To begin with, most of the experimental work is irrelevant because it dealt with doses that were much too high. Moreover, infected rats were often the experimental animals, there were no attempts to distinguish effects caused by asbestos from those caused by the almost universal opportunistic infections by mycoplasmas, and finally too much of the work used irrelevant experimental procedures like injecting the asbestos fibers into some organ or lumen.

Aside from this we can ask a few questions, speculate a little, suggest a few avenues of approach, award some bouquets, and cast a few stones. The pleural plaques contain collagen and I would expect that there would be immunofluorescent localization of globulin at these sites, but Zaidi (1) and Turner-Warwick (2) in separate studies on limited material did not find such. Do these people produce antilung connective tissue antibodies seen in other chronic pulmonary disease? Turner-Warwick has found them, but was unimpressed with the frequency in the small population of cases she has studied.

Similarly, since IgA is known to be greatly increased in miners with CWP, could one look for IgA levels in patients with asbestosis? Turner-

Warwick (2) again has followed this lead and indeed finds this to be the case in a smaller proportion than seen in CWP.

Several authors (3-5) have reported increased rheumatoid factor (RF) and antinuclear factor (ANA) in CWP, while Turner-Warwick (6) has looked for these in asbestosis cases. She finds fourfold increases in prevalence (when compared with a normal population) and suggests that since some people show a predisposition to form such autoantibodies and since the occurrence of ANA reactivity especially is related to radiographic extent of asbestosis, then routine screening for ANA in asbestos workers would be a good epidemiological tool, in that positive reactors should be discouraged from working in jobs where they would be exposed to the asbestos dusts. Pernis et al. (7) could not in one brief experiment induce RF experimentally with asbestos.

I urge great caution to those interested in looking for serum antibodies in pulmonary or intestinal exposure to environmental agents because these organs have a different immunologic system, i.e., the secretory system, than that found in the peripheral blood and is not necessarily reflected in the serum. I would suggest that investigators employ bronchial or intestinal secretions for a better picture of any immunologic response to such agents.

Perhaps a too obvious possibility, but is that naked asbestos fiber antigenic itself? My instincts would say no because silica is not, but then my instincts would have predicted that beryllium was not a good antigen either, and there is conclusive evidence that it is (8). It is obvious that the fiber can be coated with various types of innate proteins and possibly microbial

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products. I suggest that in this manner asbestos could function as an antigenic carrier or even as an adjuvant as in the case of silica. I am unaware of any investigation along these lines.

There is a report from England (unpublished) that mesothelioma tumor fluid is cytotoxic for cultured mesothelioma cells but not other cell cultures. Thus it seems to have immunologic specificity, and I find this an exciting finding. I do not believe this is any of the lymphokines because such substances would be cytotoxic for other cell cultures.

Information about cell-associated immunity (in contrast to the serum or humoral associated immunity) appears to be stronger. On the negative side, since the hyperkeratosis associated with dermally imbedded fibers disappears when the foreign body is removed, it suggests that there is no delayed hypersensitivity as in berylliosis. This may in turn be related to solubility, but I am told that asbestos fibers are indeed soluble *in vivo*.

Lymphocytes are seen infiltrating mesotheliomas and to an immunologist, such cells always suggest a cell associated immune response. Turner-Warwick has found (2) that PHA stimulation was impaired in 4 of 12 asbestosis patients. Such a test is regarded as a good way to determine T cell function in an animal, and those with immunologic deficiency syndromes of T cell origin show similar results. This suggests that, as with any tumor, mesotheliomas develop in people who develop immunologic abnormalities. For these reasons I suggest that any epidemiologic study of asbestos workers include tests for both T and B cell competence as a measure of their immune competence. The British have recognized this possibility and are proceeding ahead.

Turner-Warwick has a small bit of evidence that asbestos may be antigenic in stimulating cell-mediated immunity, as she has been able to demonstrate inhibition of macrophages in some asbestos workers when appropriate cells are incubated with asbestos fibers. This is a currently respectable technique for assessing cell-mediated responses immunologically.

In addition, let me say to those who made such statements as "you are studying it to death", "it's a human disease so let's study humans", or "John-Manville can't employ pathogen-free workers, so what good are pathogen-free animals?", I hope this sort of

thinking isn't prevalent. Had it been in the past, we would have never had vaccines, antibiotics, renal dialysis, or ball and socket prosthesis. We study asbestosis because, even if we eliminated all environmental exposure today, we would still be seeing asbestosis well into the next century. If we understand how it happens, maybe we can do something about it. As an experimentalist there is a great deal that can be done in the laboratory that is directly applicable to the human situation if the experiments are designed properly. Indeed, all of my studies are with the human in mind. I must stress the use of pathogen free animals, especially if one is using rats. The evidence is abundant that *Mycoplasmas* and other opportunistic rodent infections can cause significant changes in animals, and the experimentalist by definition must isolate one phenomenon for critical review at a time so that he may determine exactly the individual contribution of the variable he is measuring. I would suggest that (1) pathogen-free animals are being used, (2) that they are kept that way by strict quarantine measures, and (3) that the animals are constantly monitored for *Mycoplasma* infection. Similarly, since cell culture utilizing macrophages and fibroblasts will be becoming more important for study of *in vitro* effects of asbestos and silica, I suggest that in order to be believed, all experimental protocols include monitoring of the cultures for *Mycoplasma*.

REFERENCES

1. Zaidi, S. H. Experimental Pneumoconiosis, Johns Hopkins Press, Baltimore, 1969, p. 163.
2. Turner-Warwick, M. personal communication.
3. Schroeder, W., Franklin, E. C., and McEwen, C. Rheumatoid factors in patients with silicosis with round nodular fibrosis of the lung in the absence of rheumatoid arthritis. *Arth. Rheum.* 5: 10 (1962).
4. Wagner, J. C., and McCormick, J. N. Immunological investigations of coalworkers' disease, *J. Roy. Coll. Physicians (London)* 2: 49 (1967).
5. Lippmann, M., et al. Circulating antinuclear and rheumatoid factors in coal miners, *Ann. Int. Med.* 79: 807 (1973).
6. Turner-Warwick, M. Circulating rheumatoid and antinuclear factors in asbestos workers, *Brit. Med. J.* 3: 492 (1970).
7. Pernis, B., Vigliani, E. C., and Selikoff, I. Rheumatoid factor in serum of individuals exposed to asbestos, *N. Y. Acad. Sci.* 132: 112 (1965).
8. Marx, J. J., and Burrell, R. Sensitivity to beryllium compounds *J. Inorg. Nucl. Med.* 17: 173 (1973).